PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health needs of refugee children identified on arrival in reception countries – a systematic review and meta-analysis
AUTHORS	Baauw, Albertine; Kist-van Holthe, Joana; Slattery, Bridget; Heymans, Martijn; Chinapaw, Mai; van Goudoever, Hans

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting USA Competing interests: None
REVIEW RETURNED	19-May-2019

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. These were quite good but I have a couple suggestions. What was done when there was substantial heterogeneity? Line 127 Is this a 95% CI? Or what? Line 135 Compared to whom? That is who are the children being compared to? Line 140 Again, who are the South Asians being compared to? Figures - why put the fixed effect results when you are using random effects?

REVIEWER	Reviewer name: Dr Mitchell Smith Institution and Country: NSW Refugee Health Service Sydney, Australia Competing interests: None
REVIEW RETURNED	25-May-2019

GENERAL COMMENTS	Overall comments: A worthwhile review. Suggested revisions are all generally minor; however there are a lot of them, so I ticked 'major revision'. While the authors have a very good level of written English, there are many subtle wording errors, mis-spellings etc, and the article would benefit from close scrutiny by a native English speaker. Also, the overall concept of "prevalence rates" might be better framed as "detection rates", as one can't vouch for the representativeness of the different refugee child groups screened. This may have to be mentioned as a limitation as well. Specific comments: Title – 'Outcomes of health conditions..' is not clear or accurate – perhaps just "Health status of…"

	Abstract – is contradictory, as it says refugee child “health status in unknown” , but then goes on to list a range of conditions that are known.. Box 1 – the context of the last sentence of the refugee definition should be stated - i.e. only for this paper - most refugees globally do not have residence of any country. (Another term the authors might find useful for the text is “children from refugee and refugee-like backgrounds”.) Page 4 Line 107: heading is “Concerns in refugee children” but in fact this section describes global child health matters P5 L 131 Why “hetero” here? L 133 – Is there a reference for decline in TB in developed (“Western”) countries? While this is true over the longer term, in many the decline has levelled off, due to migration. L 138 should mention iron deficiency (very common globally and in refugee children) – and link this back to anaemia; this section does not mention B12 or vit D either. L 145 – very cursory description of vaccine coverage, which varies hugely across the globe. L149 – suggest split this sentence in two. ‘This will inform the development of a national…” P7 Table 1 – suggest delete Sweden & Switzerland in table, as zero papers. Table 2 – title could be clearer e.g.“reported conditions” The paper by Ngo, C (2018) only has hepatitis B listed against it – however this paper has data on strongyloides in the text, and in the supplementary tables has hepatitis B immunity by COB and age group (which could be added to Table 8), plus LTBI by age. P 9, L 222 - HBC should be HBV. P10 L261-2 – do not understand the statement that most info on “infectious diseases” came from national TB programs. Does it mean info on “active tuberculosis”? Significant caveats should be placed on the measures of schistosomiasis and strongyloides “prevalence” (‘detection rates’) using serology, as it is known this may not indicate current infection. This may need to be flagged more clearly in Table 5 as well, as otherwise an unskilled reader will get the wrong impression. Same for hepatitis C Ab positivity (which is mentioned elsewhere, but not explained i.e. does not indicate current infection necessarily). P 11 last sentence is incomplete. Table 5 – see comment above re serology. Also, ‘intestinal infections’ – it would be good to specify which ones (eg giardia etc) ,or at least examples of these; and presumably these data exclude schisto and strongy in stools? Or maybe not – needs clarification. Table 7 & 8 typo ‘ Middles East’ Table 7 ‘Intoxications’ not used in this context in English – better is “Lead poisoning” P 15 & 16 Entire Discussion needs careful edit. Third para mentions US & Canadian guidelines but not Australian ones (2016) - https://www.asid.net.au/documents/item/1225 Para at L 371 could also refer to the WHO criteria for a screening program. P 16 L 387-8 unclear. L389 not sure of point being made in sentence. Is this an argument for screening? Conclusion L 405 – need to clarify in first line that the context is resettlement countries (not refugees in general) . Lastly, the Conclusion does not refer to the initial stated aim of informing Dutch guidelines – has the Review been useful to assist

	with that?

REVIEWER	Reviewer name: Nicole Ritz Institution and Country: University Children's Hospital, Basel Competing interests: None
REVIEW RETURNED	27-May-2019

GENERAL COMMENTS	Thank you for asking me to review this interesting and important manuscript. This paper is a systematic review of the most important health conditions in refugee children. The paper covers a large area of conditions that are important for refugee children and health care workers looking after these children. Some of the reported results could be detailed a bit more and have add a couple of comments and suggestions which I feel would improve the current manuscript and analysis. 1) Title: The current title is a bit vague and I strongly suggest changing this to " Prevalence of most common health conditions in refugee children after arrival in host countries: a systematic review and meta-analysis". 2) The abstract currently does not give enough information of the results to the reader I therefore suggest shortening the introduction section to 3 shorter sentences and expand the results section. The methods section of the abstract includes results (number of potentially relevant papers and how many were selected) these should be moved to the results section. 3) I find the section of "finding and interpretation" very woolly currently and miss real results. Please include some of the most important results here eg: how many studies from how many countries; some of the prevalence data e.g. for anaemia, LTBI/active TB, intestinal infection and Vit D deficiency. 4) Some kind of interpretation of the prevalence data would be important as a conclusion in the abstract. Such prevalence data are indeed important and should guide us to what screening makes sense, but I also like the comment in line 371/372 in the discussion. So I would suggest a sentence in the conclusion that screening should be based on prevalence data but not solely and that national budgets, cost-effectiveness and personal factors of the patient should be taken into account. 5) In the introduction line 83 "about half of the refuges are children" versus the abstract saying "one third" are children. Suggest to be consistent on this fact or cite the different references. 6) The introduction is a bit unusual with all the subheadings for the topic that have been chosen for inclusion in the systematic review. I would have preferred to have a section that generally talks about which topics are of importance and shorten the sections on each disease to 1 or 2 sentences. 7) The aim of the paper is stated twice in the introduction line 104/105 and 149-151. Suggest having this only once at the end of the introduction. 8) Methods should provide the full details of the search strategy for each of the used databases as supplementary data. So each reader can follow the line of search strategy and repeat this. This is also one of the requirements if systematic reviews are done according to PRISMA guidelines. 9) Please ref the guidelines in line 156. 10) The Box 2 uses too much space and I suggest including this into the text of the methods. Two formal questions regarding the box: Why were children from the Americas (eg middle and south America excluded as potential study population), and were case series also

	excluded. 11) How did the authors excluded if health status was checked during hospital admission? Some children are routinely checked for health in hospital settings. I am not sure if this led to the exclusion of for example the following study 10.1097/INF.0b013e3182748f0b by de la Fuente et al in PIDJ 2013 reporting on tetanus immunisation coverage. 12) Line 188-193 I am not competent enough to judge if the meta-analysis was done according to standards. However, I miss I2 calculations which should be done to measure heterogeneity of the studies. Suggest formal statistical evaluation. 13) From line 195 onwards this belongs to the results section (which exception of line 198-199) 14) Table 1: Why are country listed that have not studies (Switzerland and Sweden). 15) Table. 2: This is an important table. Suggest adding the year in which the patients were investigated not only the year of the publication, as there is sometimes substantial lag between data collection and publication. In the constant changes of migration patters the years of screening are important. 16) Table 2: Also, would it be possible to list all conditions and just add an “x” for the studies that included a specific condition. This would make it much easier that the current number codes used for the conditions. 17) Table 3: Is great and the key piece of analysis! Suggest adding subheadings for the conditions as it has been mentioned in the aims for the study ie RBC conditions, infections, growth and nutrition, vaccination status. 18) Suggest to leave out the section on ESBL. Colonisation of resistant bacteria can probably not really been found well by your search criteria as these get mostly screened when someone is admitted to the hospital. There is more information and I think you would need to include other studies including MRSA and MDR-gram negatives colonisation eg by Reinheimer C Eurosurveillance 2016 which screened patients admitted from refugee accommodations for MRSA and ESBL/MDR Gram negatives. See also line 299-300. Makes no sense currently and should be left out. 19) In general, the text sections between Tables 4-8 is quite often redundant for information given in the table and difficult to follow for the reader. Suggest revising those section and only highlight a few important points. Maybe a format similar to starting each section by saying: Estimated prevalence of anaemia and hemoglobinopathies are shown in Table xy. Then describe a bit further. Currently the text in line 280-283 is difficult to follow for the reader. 20) Immunisations: any reason why de la Fuente was not included for immunisation analysis (see comment 11) 21) Discussion: Suggest referencing the EAP recommendation not only the editorial which should be available online shortly (line 360). 22) The cost-effective section is important and suggest to expand on this. We recently published a paper on TB screening in migrant children https://www.ncbi.nlm.nih.gov/pubmed/31097066, which could also be added as a reference here. 23) The section on other aspects influencing screening is important and could include a further publications (also a systematic review), which is about to be published by Brandenberger J et al in BMC public health: A systematic literature review of reported challenges in health care delivery to migrants and refugees in high-income countries – the 3C model.

	24) Conclusion: Suggest to focus more on the data that has been generated by this systematic review and what consequences can be drawn: i.e. use prevalence data for screening but not only….

VERSION 1 – AUTHOR RESPONSE

Dear Peter Blom, thank you so much for reviewing my paper. Your remarks will improve the quality of this work. I will answer your questions one by one:

What was done when there was substantial heterogeneity?

Thank you for this observation. This is indeed the case when you are working with population based data. For correct estimation of pooled prevalence rates we used random effects models taking into account substantial heterogeneity according to differences in true prevalence rates. The same was observed in other articles trying to estimate worldwide prevalences of certain conitions. for example from Schweitzer (Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386(10003):1546-55). However, theese estimates help us to develop public health policies, when for example nationwide screening programs are indicated.

Line 127 Is this a 95% CI? Or what?

Thank you, indeed not clear. This has been adjusted, line 140.

Line 135 Compared to whom? That is who are the children being compared to?

Thank you, for your observation, has been adjusted.

Line 140 Again, who are the South Asians being compared to?

Adjusted

Figures - why put the fixed effect results when you are using random effects?

Yes thank you, the random effects are used. According to our statistician is important to show both to see the difference.

Thank you Dr Mitchell Smith for reviewing my paper! Your remarks will definitely improve the quality of this paper!

While the authors have a very good level of written English, there are many subtle wording errors, mis-spellings etc, and the article would benefit from close scrutiny by a native English speaker.

Yes thank you, the paper has been revised by a native English speaker in the meantime, with services provided from the BMJ. A proof of this will be provide.

Also, the overall concept of “prevalence rates” might be better framed as “detection rates”, as one can’t vouch for the representativeness of the different refugee child groups screened. This may have to be mentioned as a limitation as well.

Yes you are right. We tried to frame it as “estimates”. We discussed this extensively in our working group. We recognize the limitation. The same has been done by Schweitzer in his article about worldwide prevalence rates of hepatitis B. He talks about ”estimates”. As you suggested it was put in the linitations.

(Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386(10003):1546-55).

Specific comments:

Title – ‘Outcomes of health conditions..’ is not clear or accurate – perhaps just “Health status of…”

Abstract – is contradictory, as it says refugee child “health status in unknown” , but then goes on to list a range of conditions that are known..

Thank you for your comment. The title has been changed.

Box 1 – the context of the last sentence of the refugee definition should be stated - i.e. only for this paper - most refugees globally do not have residence of any country. (Another term the authors might find useful for the text is “children from refugee and refugee-like backgrounds”.)

Yes thank you. We totally agree that the definitions in the literature for refugee, migrant and asylum seekers in the literature are not clear. There is no accepted definition. That is why we chose the term refugee to cover all. Line 99: In this article the term refugee children is used to describe entire child population of asylum seekers, refugees, status-holders, and undocumented migrants. Children from refugee and refugee-like backgrounds is also a widely used term. There is no universally accepted definition to describe refugee children.

Page 4 Line 107: heading is “Concerns in refugee children” but in fact this section describes global child health matters

Thank you, this has been changed

P5 L 131 Why “hetero” here? We agree, this should be removed.

L 133 – Is there a reference for decline in TB in developed (“Western”) countries? While this is true over the longer term, in many the decline has levelled off, due to migration. Thank you, reference has been changed, to refer to the global WHO report on tuberculosis.

L 138 should mention iron deficiency (very common globally and in refugee children) – and link this back to anaemia; this section does not mention B12 or vit D either.

Yes we totally agree with you, with the limitation of words, some parts were left out. It should be in here. We put it back.

L 145 – very cursory description of vaccine coverage, which varies hugely across the globe.

Yes totally agree, this is because of the limitation of words. On each of the topics we could write a full page.

L149 – suggest split this sentence in two. ‘This will inform the development of a national…”

Yes thank you, we rephrased.

P7

Table 1 – suggest delete Sweden & Switzerland in table, as zero papers.

Thank you for this remark, we deleted the rows.

Table 2 – title could be clearer e.g.“reported conditions”

Thank you we adjusted

The paper by Ngo, C (2018) only has hepatitis B listed against it – however this paper has data on strongyloides in the text, and in the supplementary tables has hepatitis B immunity by COB and age group (which could be added to Table 8), plus LTBI by age.

Yes thak you for reading carefully. In the main text only hepatitis Bprevalences could be traced back to age groups.

P 9, L 222 - HBC should be HBV.

Yes thank you, this was changed.

P10 L261-2 – do not understand the statement that most info on “infectious diseases” came from national TB programs. Does it mean info on “active tuberculosis”?

Yes, indeed, was rephrased. National TB programs are targeting active tuberculosis. From all data, the majority came from the national TB programms.

Significant caveats should be placed on the measures of schistosomiasis and strongyloides “prevalence” (‘detection rates’) using serology, as it is known this may not indicate current infection. This may need to be flagged more clearly in Table 5 as well, as otherwise an unskilled reader will get the wrong impression.

Totally agree, same for intestinal infections, it does not indicate we all need to treat. I will try to add a sentence on that. Line 317, rephrased: Positive serology can be a sign of past or present infection.

Same for hepatitis C Ab positivity (which is mentioned elsewhere, but not explained i.e. does not indicate current infection necessarily). Positive serology can be an indicator for both past or active infection and requires further evaluation.

P 11 last sentence is incomplete.

Table 5 – see comment above re serology. Also, ‘intestinal infections’ – it would be good to specify which ones (eg giardia etc) ,or at least examples of these; and presumably these data exclude schisto and strongy in stools? Or maybe not – needs clarification.

Yes in fact I strongly agree, but the problem is space and words. Actually this could be an article in itselve. Especially the differences in countreis were preseumptive treatment is given. We will work on this. After long discussions with our group, we decided to leave it like this.

Table 7 & 8 typo ‘ Middles East’

Thank you we changed

Table 7 ‘Intoxications’ not used in this context in English – better is “Lead poisoning”

Thank you we changed

P 15 & 16 Entire Discussion needs careful edit.

Third para mentions US & Canadian guidelines but not Australian ones (2016) - https://www.asid.net.au/documents/item/1225

Thank you for the advice. Indeed, more national policies exists. I could not mention them all.

Para at L 371 could also refer to the WHO criteria for a screening program.

Agreed, the criteria from Jungner and Wilson were added. In the original version we included al the screening criteria of Wilson and Jungner but due to lack of space, we left it out. You are right it deserves a space here.

P 16 L 387-8 unclear.

Thank you indeed, this sentence has been rephrased.

L389 not sure of point being made in sentence. Is this an argument for screening?

Thanks for this remark. This sentience has been moved to 374.

Conclusion L 405 – need to clarify in first line that the context is resettlement countries (not refugees in general) .

This has been adjusted. In line 403 we stated the effect of this systematic review on the Dutch situation.

Lastly, the Conclusion does not refer to the initial stated aim of informing Dutch guidelines – has the Review been useful to assist with that?

Yes indeed, it has! We are in the process of developing a multi disciplinairy health assessment guideline.

Dear Nicole Ritz, thank you for editing and reviewing our paper so extensively. Your suggestions contributed to a great extend to the quality of this paper.

1) Title: The current title is a bit vague and I strongly suggest changing this to

“ Prevalence of most common health conditions in refugee children after arrival in host countries: a systematic review and meta-analysis”.

Thank you so much for your extensive review and recommendations. Your analysis of the paper will definitely improve the quality of this paper.

The title has been changed, thanks to your suggestion and the suggestion of the editor in chief

2) The abstract currently does not give enough information of the results to the reader I therefore suggest shortening the introduction section to 3 shorter sentences and expand the results section. The methods section of the abstract includes results (number of potentially relevant papers and how many were selected) these should be moved to the results section.

Thank you for your advice. The abstract was rewritten, and the introduction was shortened.

3) I find the section of “finding and interpretation” very woolly currently and miss real results. Please include some of the most important results here eg: how many studies from how many countries; some of the prevalence data e.g. for anaemia, LTBI/active TB, intestinal infection and Vit D deficiency

Thank you for your advice, the introduction was adjusted

4) Some kind of interpretation of the prevalence data would be important as a conclusion in the abstract. Such prevalence data are indeed important and should guide us to what screening makes sense, but I also like the comment in line 371/372 in the discussion. So I would suggest a sentence in the conclusion that screening should be based on prevalence data but not solely and that national budgets, cost-effectiveness and personal factors of the patient should be taken into account.

Thank you, this has been added to the conclusion line 79 and 80.

5) In the introduction line 83 “about half of the refuges are children” versus the abstract saying “one third” are children. Suggest to be consistent on this fact or cite the different references.

Is true, the worldwide figures of refugees are different from the European context.

6) The introduction is a bit unusual with all the subheadings for the topic that have been chosen for inclusion in the systematic review. I would have preferred to have a section that generally talks about which topics are of importance and shorten the sections on each disease to 1 or 2 sentences.

Yes you are right, this section has been rewritten several times. When we put everything in the same introduction, the topic will be very blurry. Throughout the article we have tried to consequently divide in 4 sub groups.

7) The aim of the paper is stated twice in the introduction line 104/105 and 149-151. Suggest having this only once at the end of the introduction.

Thank you, is indeed double, we deleted line 149-151.

8) Methods should provide the full details of the search strategy for each of the used databases as supplementary data. So each reader can follow the line of search strategy and repeat this. This is also one of the requirements if systematic reviews are done according to PRISMA guidelines. Yes thank you, we adjusted the text.

9) Please ref the guidelines in line 156.

Yes the reference was added.

10) The Box 2 uses too much space and I suggest including this into the text of the methods. Two formal questions regarding the box: Why were children from the Americas (eg middle and south America excluded as potential study population), and were case series also excluded.

Thank you for reading this carefully. Children from the Americas were excluded because these children are hardly seen as refugee entering the Netherlands. We had the feeling we had to limit our search to a certain extent. It could have been included as well as the eastern European countries. This was a decision taken in the beginning of the study.

11) How did the authors excluded if health status was checked during hospital admission? Some children are routinely checked for health in hospital settings. I am not sure if this led to the exclusion of for example the following study 10.1097/INF.0b013e3182748f0b by de la Fuente et al in PIDJ 2013 reporting on tetanus immunisation coverage.

Yes you are right, we excluded studies when children were checked during hospital admission, because we were interested in population based figures. This was done to avoid selection bias.

12) Line 188-193 I am not competent enough to judge if the meta-analysis was done according to standards. However, I miss I2 calculations which should be done to measure heterogeneity of the studies. Suggest formal statistical evaluation.

13) From line 195 onwards this belongs to the results section (which exception of line 198-199)

Thank you the heading was changed to another location

14) Table 1: Why are country listed that have not studies (Switzerland and Sweden).

Thank you has been removed.

15) Table. 2: This is an important table. Suggest adding the year in which the patients were investigated not only the year of the publication, as there is sometimes substantial lag between data collection and publication. In the constant changes of migration patters the years of screening are important.

Table was rearranged according to reception country.

16) Table 2: Also, would it be possible to list all conditions and just add an “x” for the studies that included a specific condition. This would make it much easier that the current number codes used for the conditions.

Yes, we experienced with this and another reviewer was not in favour. The table needs then 23 rows extra, so this was not feasible.

17) Table 3: Is great and the key piece of analysis! Suggest adding subheadings for the conditions as it has been mentioned in the aims for the study ie RBC conditions, infections, growth and nutrition, vaccination status.

Good suggestion! Thank you, this is indeed the masterpiece of my work of the last 3 years. We rewrote the table, and made subheading. Great! This looks better.

18) Suggest to leave out the section on ESBL. Colonisation of resistant bacteria can probably not really been found well by your search criteria as these get mostly screened when someone is admitted to the hospital. There is more information and I think you would need to include other studies including MRSA and MDR-gram negatives colonisation eg by Reinheimer C Eurosurveillance 2016 which screened patients admitted from refugee accommodations for MRSA and ESBL/MDR Gram negatives. See also line 299-300. Makes no sense currently and should be left out.

Thank you, we removed all the information on ESBL

19) In general, the text sections between Tables 4-8 is quite often redundant for information given in the table and difficult to follow for the reader. Suggest revising those section and only highlight a few important points. Maybe a format similar to starting each section by saying: Estimated prevalence of anaemia and hemoglobinopathies are shown in Table xy. Then describe a bit further. Currently the text in line 280-283 is difficult to follow for the reader.

Thanks for your advice. The text was rephrased.

20) Immunisations: any reason why de la Fuente was not included for immunisation analysis (see comment 11)

Yes, because these were hospital based figures and were left out to avoid bias.

21) Discussion: Suggest referencing the EAP recommendation not only the editorial which should be available online shortly (line 360).

This was added

22) The cost-effective section is important and suggest to expand on this. We recently published a paper on TB screening in migrant children https://www.ncbi.nlm.nih.gov/pubmed/31097066, which could also be added as a reference here.

Thank you, this was added.

23) The section on other aspects influencing screening is important and could include a further publications (also a systematic review), which is about to be published by Brandenberger J et al in BMC public health: A systematic literature review of reported challenges in health care delivery to migrants and refugees in high-income countries – the 3C model.

24) Conclusion: Suggest to focus more on the data that has been generated by this systematic review and what consequences can be drawn: i.e. use prevalence data for screening but not only….

Thank you so much for your extensive edits of our paper. The quality of this paper was increased considerably.